Clinical studies with new dopamine agonists

Girbes, Armand Roelof Johan

SUMMARY

Dopamine, a naturally occurring catecholamine is extensively used in the intensive care setting. Dopamine exerts a complicated influence on the cardiovascular and renal system. This is due to the fact that dopamine stimulates different types of adrenergic receptors: not only α- and ß-adrenergic but also specific dopamine receptors. And each of these receptors can be divided in two subtypes according to the effects exerted by their stimulation. Dopamine can be applied for various indications depending on the given dose. This is due to the amount of stimulation and the change of balance of these receptor effects for different doses. In doses of 1-4 μg/kg/min, nicknamed "renal dose", the predominant effect of dopamine is a marked increase of renal plasma flow, glomerular filtration rate and sodium excretion. This is mainly caused by stimulation of dopamine-receptors. In doses of 4-10 μg/kg/min dopamine exerts positive inotropic effects, primarily as a result of ß-(1)-receptor stimulation. In doses of above 10 μg/kg/min dopamine induces vasoconstriction and positive chronotropism as a result of predominant α-adrenergic and ß-adrenergic effects, respectively. The scheme sketched above for different doses of dopamine is in fact a simplification of a balance of counteracting effects of stimulation of different receptors by dopamine.

Dopamine receptors are present at various sites of the body, not only in the Central Nervous System (CNS), but also outside the CNS, the so called peripheral dopamine receptors. These receptors are divided in two types: postsynaptic DA1, and (presynaptic) DA2 receptors. DA1 receptors are located in blood vessels and in the proximal tubule of the kidney. Stimulation induces vasodilation and natriuresis. The DA2 receptors are situated prejunctionally on sympathetic nerve terminals and in the adrenal gland. Stimulation of DA2-dopamine receptors results in inhibition of norepinephrine release and inhibition of aldosterone secretion.

More widespread use of dopamine (agonists) is limited because of a lack of oral availability. In recent years some orally active dopamine agonists have become available for clinical studies. This thesis describes renal and neurohumoral effects of two new dopamine agonists.

In **chapter 1** an extensive review of the literature is given with recent views on the different dopamine-receptors. Aspects of intracellular transduction mechanisms after stimulation of dopamine receptors are discussed. In earlier studies some evidence was found that abnormalities of endogenous dopamine release or dopamine receptors are present in hypertension - and possibly heart failure. Currently, animal studies suggest post-receptor defects of dopamine-receptors in animal models for essential hypertension.

With diverse techniques dopamine-receptors can now be localized. The presence of DA1-receptors in different vascular beds and the renal proximal tubule is now established. DA2-receptors are unequivocally recognized prejunctionally on sympathetic

nerve terminals and in the adrenal gland. However, with regard to the ganglionic dopamine-receptors, the question of receptor subtypes involved, still needs to be resolved.

Subsequently, fenoldopam, a selective DA1-receptor agonist, and ibopamine, an aselective dopamine agonist with α- and ß-adrenergic activity are discussed. Short attention is given to dopexamine, an aselective dopamine- and ß2-agonist, which is for intravenous use only.

Fenoldopam induces vasodilatation with a fall in systemic vascular resistance and increase of cardiac output, a pronounced increase of renal blood flow and natriuresis, the latter being (partially) induced by stimulation of proximal tubular DA1-receptors. The clinical applications therefore appear to be hypertension and especially hypertensive emergencies, and heart failure.

Ibopamine, a prodrug, is the di-isobutyryl ester of methyl-dopamine (epinine) and is de-esterified to epinine after oral administration. Epinine, stimulates α-, ß-adrenergic and DA1- and DA2-dopamine receptors. Oral administration of ibopamine in normal man has been reported to result in an increase of sodium excretion and creatinine clearance, without changes in heart rate and blood pressure. In patients with congestive heart failure, ibopamine improves the hemodynamic parameters with an increase of cardiac index, and a fall of systemic- and pulmonary vascular resistance.

Additionally, the effects of ibopamine on plasma norepinephrine are discussed. Considering the lack of effect on blood pressure, ibopamine plays no role in the treatment of hypertension, in contrast to fenoldopam.

Finally, future perspectives for clinical applications of dopamine agonists, are discussed. A diuretic and natriuretic drug, which increases renal blood flow, but also induces some degree of systemic vasodilatation, appears to be a promising addition to the current therapeutic tools. One might expect that ibopamine, fenoldopam and dopexamine can play an additional role in the treatment of heart failure. Several studies indicate that fenoldopam possesses a favorable profile in the treatment of severe hypertension, compared to nitroprusside.

Chapter 2 describes the renal and neurohumoral effects of i.v. fenoldopam in ascending doses, in healthy volunteers. The influence of the aselective dopamine antagonist metoclopramide on fenoldopam-induced changes was also investigated. During fenoldopam infusion the diastolic blood pressure fell slightly, with a rise in heart rate. Renal blood flow increased markedly, while the GFR remained unchanged. These effects of fenoldopam were not altered by metoclopramide. Fenoldopam induced an increase of sodium excretion, which was abolished by metoclopramide. A pronounced rise of PRA during fenoldopam infusion was found, which was blunted by metoclopramide. This rise of PRA is probably not only a compensatory reflex to the fall in blood pressure due to fenoldopam, but also a result of direct stimulation of juxtaglomerular cells. Metoclopramide induced a marked increase of aldosterone, sustained, but blunted during subsequent fenoldopam infusion, suggesting a DA1-receptor mediated

influence on aldosterone s
served during fenoldopam,
metoclopramide no change
dopam induces systemic an
effects are counteracted by
(RAAS) as evidenced by
sympathetic nervous system
studies with dopamine no
Whether the counteracting
fenoldopam, remains subje
Ibopamine as an aselective
if the DA2-receptor stimula
tion following DA1-recepto
investigated the renal and
study setting, again in norm
been completed, no studies
sodium excretion had been
on renal function and neu
induced a moderate and tra
ramide. No changes in renal
of simultaneous DA1- and α
tion. Ibopamine induced a
sodium excretion. The fall
versed by ibopamine. Ibopa
norepinephrine. The meto
blunted by ibopamine. We
GFR and natriuresis. The
probably by direct stimulati

Lithium is commonly used
evidence was provided that
the renal tubule: the natri
abolished by lithium. In **chap**
ic - response to fenoldopam
tion, sodium excretion, PR
during fenoldopam infusion
fact that lithium did not influ
it did during gludopa admini
a non-DA1-receptor mediat
while in the gludopa study 7
a dose related effect of lit
lithium with renal tubular d

influence on aldosterone secretion. An increase of plasma norepinephrine was observed during fenoldopam, while during the combined infusion of fenoldopam and metoclopramide no changes of norepinephrine occurred. We concluded that fenoldopam induces systemic and renal vasodilation but only moderate natriuresis. These effects are counteracted by activation of the Renin-Angiotensin-Aldosterone-System (RAAS) as evidenced by a rise of PRA, and subsequently aldosterone, and the sympathetic nervous system (SNS), reflected in the rise of norepinephrine. In previous studies with dopamine no such effects on RAAS and SNS have been observed. Whether the counteracting mechanisms will largely obscure the primary effects of fenoldopam, remains subject for further studies.

Ibopamine as an aselective dopamine agonist may compare favorably with fenoldopam if the DA2-receptor stimulation by ibopamine would limit the RAAS and SNS activation following DA1-receptor stimulation. Therefore, after the fenoldopam study, we investigated the renal and neurohumoral effects of oral ibopamine in a comparable study setting, again in normal man. Although numerous studies with ibopamine have been completed, no studies addressing simultaneously the GFR, renal blood flow and sodium excretion had been performed. **Chapter 3** describes the effects of ibopamine on renal function and neurohumoral parameters in healthy volunteers. Ibopamine induced a moderate and transient increase of GFR, which was abolished by metoclopramide. No changes in renal blood flow were observed. This may be the consequence of simultaneous DA1- and α-receptor stimulation or only weak DA1-receptor stimulation. Ibopamine induced a modest but significant increase of absolute and fractional sodium excretion. The fall in sodium excretion due to metoclopramide was not reversed by ibopamine. Ibopamine did not cause any changes in PRA, aldosterone and norepinephrine. The metoclopramide-induced rise of aldosterone was markedly blunted by ibopamine. We concluded that ibopamine induces a transient increase of GFR and natriuresis. The latter is not caused by renal hemodynamic effects, but probably by direct stimulation of tubular DA1-receptors in the kidney.

Lithium is commonly used as a marker of proximal tubule function. In a recent study, evidence was provided that lithium interacts with dopamine receptors at the level of the renal tubule: the natriuresis induced by the dopamine prodrug gludopa, was abolished by lithium. In **chapter 4** the lack of effect of lithium on the renal - natriuretic - response to fenoldopam in normal man is described. In this study renal vasodilation, sodium excretion, PRA and aldosterone were assessed. The increase of PRA during fenoldopam infusion, was more pronounced in the presence of lithium. The fact that lithium did not influence the natriuresis during fenoldopam infusion, whereas it did during gludopa administration might be lithium-dose related, or be explained by a non-DA1-receptor mediated mechanism. In our study 300 mg lithium was used, while in the gludopa study 750 mg lithium was used. Thus, although we cannot exclude a dose related effect of lithium, our results do not substantiate an interaction of lithium with renal tubular dopamine receptors.

Chapter 5 describes the acute renal and neurohumoral effects of 100 mg ibopamine in patients with severe congestive heart failure. From studies, performed in the seventies, we can learn that the renal effects of dopamine are more pronounced in patients with congestive heart failure, compared to normals. For this reason we performed this study, bearing in mind the results as described in chapter 3. All patients used ACE-inhibitors, digoxin and diuretics. In this group of patients, an increase of both GFR and renal blood flow was observed after the administration of ibopamine. The filtration fraction, which was markedly increased even despite the use of ACE-inhibitors, remained unchanged. No changes in blood pressure, heart rate, PRA and aldosterone were observed. A possible effect on norepinephrine could not be fully evaluated, due to a sampling error in some patients. The sodium excretion was very low in these patients, and ibopamine did not induce any clinically significant increase of the natriuresis. Probably the increase of GFR and renal blood flow is the result of both a rise in cardiac output and a systemic and renal vasodilation. Although we realize that this study was not controlled, we conclude that the renal hemodynamic results suggest that the disappointing effects observed in normal volunteers, should not be extrapolated to patients with congestive heart failure.

Another example of the different effects of dopamine receptor stimulation in healthy subjects versus patients with congestive heart failure is provided by the reported results of ibopamine on plasma norepinephrine. According to the literature ibopamine lowers plasma norepinephrine in patients with congestive heart failure. This is probably due to presynaptic DA2-receptor stimulation and additionally, this may be the consequence of an improved hemodynamic situation of the patient. In our study, described in chapter 3, we observed no changes in plasma norepinephrine caused by ibopamine in healthy subjects. Since we know from the literature that patients with heart failure have an increased sympathetic drive, and in our healthy volunteers this drive was reduced to a minimum, we hypothesized that the DA2-receptor effect of ibopamine would only be apparent during sympathetic stimulation. In **chapter 6** the effects of ibopamine on exercise-induced increases of catecholamines in healthy subjects are described. Maximal oxygen consumption (VO_2max) was determined using a bicycle ergometric test. Subsequently, on two separate occasions, plasma catecholamines were determined, after placebo or ibopamine. A graded exercise test was performed up to 90% of the predetermined VO_2max level. As expected a rise of systolic- and mean blood pressure, heart rate, norepinephrine and epinephrine level, with a fall in diastolic blood pressure was found. No differences for blood pressure, heart rate and epinephrine between the placebo- and ibopamine study day were found. However, the rise of norepinephrine was significantly blunted by ibopamine, compared with placebo, in accordance with our hypothesis.

The development of dopamine agonists is ongoing, with special attention to its oral availability. The recent availability of SIM2055 for clinical studies is an example of this progress. The presented data suggest that for chronic treatment, as in hyperten-

sion and heart failure, sim
advantageous. Data from in
tion of DA1- and DA2-re
simultaneous DA1- & DA
receptor mediated effects n
The field of research on dc
the dopamine-receptor-mec

sion and heart failure, simultaneous DA1- and DA2-receptor stimulation may be advantageous. Data from in vitro studies as well as clinical studies suggest an interaction of DA1- and DA2-receptors. Therefore studies comparing unique DA1- and simultaneous DA1- & DA2-receptor stimulation are required. Furthermore, DA-receptor mediated effects might be dependent on the salt-loading of the subject.
The field of research on dopamine receptors and dopaminergic drugs is challenging, the dopamine-receptor-mediated effects are promising for clinical applications.